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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010-5422

AEHA

PHASE 2
DERMAL PENETRATION AND DISTRIBUTION OF ^{14}C-LABELED
ETHYLENE DIAMINE DINITRATE
STUDY NO. 75-51-0379-85
APRIL - JULY 1984

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER 75-51-0379-85	2. GOVT ACCESSION NO. A147361	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Phase 2, Dermal Penetration and Distribution of ^{14}C-Labeled Ethylene Diamine Dinitrate, Study No. 75-51-0379-85		5. TYPE OF REPORT & PERIOD COVERED Phase 2, April - July 1984
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) Hubert L. Snodgrass, Jr.		8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS Commander US Army Environmental Hygiene Agency Aberdeen Proving Ground, MD 21010-5422		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
11. CONTROLLING OFFICE NAME AND ADDRESS Commander US Army Health Services Command Ft Sam Houston, TX 78234-5000		12. REPORT DATE April - July 1984
		13. NUMBER OF PAGES 13
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release; distribution unlimited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

C14-

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Absorption	Dog	Penetration	Topical
^{14}C-Labeled	Ethylene Diamine Dinitrate	Percutaneous	
Dermal	Excretion	Radiolabeled	
Dinitrate	Explosive	Rat	
Distribution	Intravenous	Tissues	

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Ethylene diamine dinitrate (EDDN) is an explosives component having potential for occupational skin exposure. The dermal absorption and resulting bodily distribution was assessed in rats and dogs. In both species, less than 1 percent of the applied ^{14}C-labeled dose was absorbed as measured by radioactivity appearing in excreta through 7 days. About 1.5 percent remained in animal carcasses at necropsy. Retention was not organ specific. In man, less than 2 percent absorption is expected following a single dermal exposure. No significant tissue retention is anticipated.

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

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Mr. Snodgrass/cvc/AUTOVON
584-3980

REPLY TO
ATTENTION OF

HSHB-OT/WP

31 OCT 1984

SUBJECT: Phase 2, Dermal Penetration and Distribution of ^{14}C-Labeled Ethylene Diamine Dinitrate, Study No. 75-51-0379-85, April - July 1984

Commander
US Army Materiel Command
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Copies of subject report with Executive Summary are inclosed.

FOR THE COMMANDER:

1 Incl
as

for [signature] LTC
JOEL C. GAYDOS, M.D.
Colonel, MC
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CF:
HQDA (DASG-PSP) wo incl
Cdr, ARDC (AMDAR-LCE-D)
Cdr, HSC (HSCL-P)
Comdt, AHS (HSHA-IPM)
Cdr, MEDDAC, Ft Monmouth (PVNTMED Svc) (2 cy)
Cdr, WRAMC (PVNTMED Svc)
C, USAEHA-Rgn Div North
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EXECUTIVE SUMMARY
PHASE 2
DERMAL PENETRATION AND DISTRIBUTION OF ^{14}C-LABELED ETHYLENE DIAMINE DINITRATE
STUDY NO. 75-51-0379-85
APRIL - JULY 1984

1. PURPOSE. The formulation for a new series of explosives contains 40 percent of ethylene diamine dinitrate (EDDN). Occupational skin contact in man is likely. As such, the cutaneous absorption potential and bodily distribution of EDDN was assessed in animals using the radiolabeled (^{14}C) chemical.

2. ESSENTIAL FINDINGS. Radiolabeled EDDN (400 µg) in aqueous solution was applied to the skin of rats and dogs. Absorption was minimal, measuring about 2 percent of the applied dose in rats and 1 percent in dogs through 7 days. Urinary excretion accounted for nearly all of the recovered radiolabeled chemical in dogs. In rats, absorbed radiochemical also appeared in the urine but residual radioactivity remained in the carcasses at necropsy. However, no marked tissue deposition of ^{14}C-labeled EDDN moieties was observed in dogs for the same period. Following a single intravenous injection (400 µg) to both species, almost all of the recovered radioactivity appeared in urine within 24-48 hours. At necropsy, 7 days after injection, significant levels of radioactivity were measured in tissues from both species.

3. CONCLUSIONS. The dermal absorption of EDDN in man would be expected to be equal to or lower than that demonstrated in animals, probably less than 2 percent of the applied dose. Urinary excretion is the major pathway of metabolic elimination of absorbed chemical. Little, if any, tissue deposition would be expected at the topical dose level tested, 400 µg/cm^2. Some bodily retention of systemic EDDN could occur from alternate routes of exposure, perhaps 5 percent of the total dose. Human-use hazard recommendations must await corroborative animal toxicity data.

DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
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PHASE 2
DERMAL PENETRATION AND DISTRIBUTION OF ^{14}C-LABELED ETHYLENE DIAMINE DINITRATE
STUDY NO. 75-51-0379-85
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1. AUTHORITY.

a. Letter, DRDAR-LCE-D, US Army Armament Research and Development Command, 28 April 1982, subject: Toxicology Study of Ethylene Diamine Dinitrate, and indorsement thereto.

b. Letter, DRDAC-LCE-D, US Army Armament Research and Development Command, 14 June 1983, Concerning the substitution of the DEAK formulation for NEAK.

2. REFERENCE. Toxicology Division Standing Operating Procedure, Radioisotope Studies, US Army Environmental Hygiene Agency (USAEHA), March 1984.

3. PURPOSE. The purpose of this study was to quantitate the rate of absorption of ^{14}C-labeled ethylene diamine dinitrate (EDDN) following a single topical application in rats and dogs. Animals were also treated intravenously with the radiochemical to maximize bioavailability and for kinetic measurements. The potential for chemical retention in the body and elimination kinetics was also assessed. The methodology for evaluating skin penetration in animals has been previously described in the reference.

4. SPONSOR. US Army Armament Research and Development Command, Dover, New Jersey, ATTN: DRDAR-LCE-D.

5. GENERAL.

a. See Appendix A for the Bibliography.

b. See Appendix B for Analytical Quality Assurance information.

6. BACKGROUND.

a. A new series of explosives containing EDDN is being developed by ARRADCOM and the Air Force. The formulation of interest, DEAK, contains 40 percent EDDN. Appropriate safety precautions and handling procedures for operational personnel precludes DOD's interim use approval. The likelihood of skin contact in man and the absence of applicable toxicity data necessitates quantitative absorption studies.

b. The Beagle dog was selected as an animal model because it more closely resembles man's skin absorption kinetics. The albino rat was also used because of its tendency to maximize absorption of topical chemicals and for its value in demonstrating retention potential of test chemical within the body.

7. MATERIALS. Radiolabeled ethylene diamine (1,2-^{14}C) dinitrate, lot number 1788-134, was purchased from New England Nuclear (NEN), Boston, Massachusetts. Reported radiochemical purity was greater than 97 percent. Chemical purity was verified against a pure product standard. The specific radiocarbon activity of EDDN was 4.46 millicuries per millimole. Subsequent dilutions used laboratory distilled water.

8. ANIMALS.

a. Twelve male rats, weighing between 280 and 340 g, were randomly selected from the US Army Environmental Hygiene Agency (USAEHA) breeding colony. Animals were offspring of Charles River Sprague-Dawley COBS rats, purchased originally from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Animals were housed in individual Nalgene metabolism cages and received food (Formulab Chow #5008, Ralston Purina Company, St. Louis, Missouri) and water ad libitum. Six rats received the test compound dermally and six intravenously.

b. Six purebred Beagle dogs, 18 months old, were selected from USAEHA kennel stock. Animals were originally purchased from Laboratory Research Enterprises, Kalamazoo, Michigan. Dogs were housed in individual Wahmann metabolism cages and received food (Respond 2000, ProPet, Inc., Syracuse, New York) and water ad libitum. Three dogs were treated dermally and three intravenously.

9. METHODS.

a. Six rats each received a single intravenous injection of ^{14}C-labeled EDDN to assure that systemic elimination of the chemical was measurable in excreted urine. Injection was made into the femoral vein while the animal was under light halothane anesthesia. Each rat received 400 micrograms (μg) of labeled EDDN contained in a 0.05 mL injection volume. Radioactivity was 9.58 microcuries (μCi) per dose.

b. Six rats each received the chemical topically as a single dose. The mid-lumbar area of the animal's back was clipped free of hair and the application area demarcated with petrolatum to contain the chemical within the predetermined 1.0 cm^2 area. The applied dose was 400 µg (9.58 µCi radioactivity) which equaled an application rate of 400 $\mu g/cm^2$. To facilitate the adherence of the chemical (in water solution) to the animal's back, 1 or 2 drops of reagent grade methanol was added to the surface of the liquid dose. Using a hair dryer (no heat), a continuous stream of air was passed over the site until danger of run-off was minimal; about 5 minutes. The application area was then covered with a nonocclusive (breathable) patch which protected the area without contacting the radiochemical. The patch was changed at 24 hours.

c. Dogs also received radiolabeled EDDN as a single intravenous or topical dose. Three dogs were treated intravenously with 400 µg of the chemical. Injection of 1.0 mL, was made into the cephalic vein. The remaining three dogs each received a 400 µg dose topically to a 1.0 cm^2 area. The area was treated, as with the rats, to minimize run-off and covered with a nonocclusive patch. Each dog received a radioactive dose of 9.58 µCi.

d. Blood specimens were collected at timed intervals from dogs following EDDN injection to assess the disappearance rate of radiocarbon from circulating blood. A semilog plot of plasma radioactivity versus time was constructed using the "stripping" technique.[1] The half-life ($t_{1/2}$) was determined for the rapid distribution (alpha) phase and the slower elimination (beta) phase.

e. Excreta was collected and measured from all animals at 24-hour intervals through the 7-day test period. Aliquots (0.2 mL) of urine were combined with 15 mL of PCS®II scintillation cocktail and radioactivity measured using a Beckman Model LS 9000 Liquid Scintillation Counter. Internal standardization techniques and quench correction procedures were employed. Feces were collected daily, weighed, and combined with 2 volumes of distilled water. After mixing for 24 hours, aliquots (0.2 mL) of the supernate were combined with PCS II and counted.

f. At the end of the study period, all animals were euthanized and representative tissue and fluid specimens collected and measured for radiocarbon content. Specimens included liver, lung, kidney, spleen, heart, brain and adrenal glands. Also collected were urinary bladder, muscle, bone, skin, fat, thyroid gland, testes, bone marrow, blood and bile. Radioactivity was assessed following oxidation of each 0.25 - 0.45 g specimen to $^{14}CO_2$ using a Packard Biological Materials Oxidizer. The remaining rat carcasses were homogenized in 300 mL of distilled water to assess residual radioactivity. About 0.4 g of each homogenate was combined with 3.0 mL of Protosol®, a tissue solubilizer. The mixture was incubated at 50°C overnight. After cooling, 0.2 mL of 30 percent hydrogen peroxide was added to decolorize then the entire mixture combined with 15 mL of PCS II for scintillation counting.

® PCS II is a registered tradename of Amersham Corp., Arlington Heights, Illinois.
® Protosol is a registered tradename of New England Nuclear, Boston, Massachusetts.

g. Unabsorbed EDDN for topically treated animals was quantitated by extracting the nonocclusive patches and the excised skin from the application site in distilled water. Extract fractions, 0.2 mL, were combined with PCS II and counted.

h. Excretion rates of radiocarbon were calculated as the percent recovery each day of the injected or applied dose appearing in urine or feces. Calculations for tissue specimens collected at necropsy were based on dpm per gram of wet tissue and reported as nanogram equivalents of EDDN per gram.

10. RESULTS.

a. The fate of ^{14}C-labeled EDDN in rats following an intravenous injection is summarized in Table C-1. Urinary excretion was the major elimination pathway, accounting for 58 percent of the injected dose. Nearly all of the radioactivity appearing in urine occurred within 24 hours of injection; 2.2 percent of the dose was eliminated in urine during the remaining 6 days. Enteric elimination, radioactivity recovered in feces, measured less than 2 percent of the injected dose through 7 days. At necropsy the major internal organs and remaining carcasses contained 1 and 11 percent of the administered dose, respectively. Table C-2 summarizes the distribution of radioactivity from various tissue specimens collected at necropsy.

b. In dogs treated intravenously with ^{14}C EDDN, urinary elimination accounted for most of the excreted dose (see Table C-3). Thirty-one percent of the injected dose was recovered in urine through 7 days. Unlike rats, significant urinary clearance in dogs extended to 48 hours after injection. Radioactivity registered in feces was marginal through 7 days, contributing about 1 percent of the injected dose. Table C-2 shows the tissue distribution of radiocarbon in dogs 7 days after EDDN injection which cumulatively amounted to 2.5 percent of the dose.

c. The half-life ($t_{1/2}$) disappearance of radioactivity from circulating dog blood following parenteral ^{14}C EDDN was 14 minutes for the rapid distribution or alpha phase. The slower elimination or beta phase $t_{1/2}$ was about 131 hours.

d. The urinary excretion of radioactivity in rats and dogs following a single topical application of ^{14}C EDDN is summarized in Table C-4. The compound was minimally absorbed by either species. In rats and dogs less than 1 percent of the applied dose appeared in urine through 7 days. No radioactivity above normal background levels was detected in any feces specimen. Table C-5 represents the fate or recovery of radiocarbon from each parameter measured. Absorbed ^{14}C EDDN by the rat measured 2 percent through 7 days. In the dog, 0.8 percent was absorbed but no measurements of residual radiocarbon in the carcasses were made. Significant radioactivity was recovered from the nonocclusive patches and from unabsorbed compound remaining on the skin surface 7 days after application. Since the foam patches did not contact the test skin site, the recovery of radiocarbon from these appliances represents trapped evaporating compound or exfoliated skin from the application area. Tissue distribution of radioactivity from topically treated animals is presented in Table C-2. Only trace amounts of radiocarbon were detected in any dog tissue specimen. In rats, only the heart and bone marrow specimens contained radioactivity significantly higher than comparable terminal blood specimens.

11. DISCUSSION.

a. The skin absorption of EDDN in both animal species tested was minimal. This is of particular significance in the rat which is generally considered a maximum absorber of topical compounds and often used in predicting worst-case situations. Conversely, the dog is considered more predictive of human skin absorption kinetics.[2,3] It is reasonable to assume that the potential for human absorption of EDDN would be equal to or less than that demonstrated in animals owing to man's comparatively greater resistance to topical insult.[4] This should at least hold true within the given conditions of this study.

b. The dermal barrier appears very effective in limiting the rate of EDDN penetration, particularly in the dog. Whether or not this can be attributed to first-pass epidermal metabolism of the chemical or merely a factor of diffusion physics is not known. Radiochemical techniques cannot distinguish between EDDN and its metabolites.

c. The low molecular weight and hydrophilic nature of EDDN may also contribute to its limited absorption potential. But it also tends to enhance its persistence within the body once it reaches the systemic circulation. The pattern of tissue deposition of labeled moieties after EDDN injection and the long (beta phase) plasma half-life in dogs is suggestive of plasma protein binding. Although this should not present a problem dermally, other routes of chronic exposure such as ingestion or inhalation could prove troublesome.

d. Currently, little if any toxicological data exists for EDDN. The metabolism and pharmacokinetics of ^{14}C-labeled ethylenediamine (EDA), structurally identical to EDDN but lacking the nitrate esters, have been reported.[5] In that study, rats injected intravenously with EDA demonstrated nearly identical urinary excretion and deposition patterns as reported here for EDDN. Significant (8 percent) expiratory elimination as $^{14}CO_2$ was also observed. The major urinary metabolite of EDA was identified as N-acetylethylenediamine (AcEDA), accounting for about 50 percent of the urinary radioactivity. Lesser amounts of the parent compound were also recovered and an additional metabolite, aminoacetylaldehyde, was suggested. Interestingly, as the injected doses were elevated, a greater proportion of intact EDA was noted in urine compared to metabolite fractions. In all probability, EDDN follows a similar biotransformation pathway as EDA, the nitrate esters (EDDN) undergoing hydrolysis[6] or conjugation _in vivo_.[7]

e. The incomplete recovery of radioactivity from animals treated topically with EDDN can be attributed to evaporation of the compound from the skin surface. The nonocclusive patches, while preventing accidental contact with the test site, allow ambient air flow across the skin. Following intravenous injection of the radiochemical, significant radioactivity remained unaccountable in the dog. Respiratory elimination, not measured in the present study, may have been responsible for the lost activity as noted with EDA.[5] An additional, unknown quantity of radiocarbon is invariably lost in the excreta collection processes. This is magnified in the later collection periods where radioactivity levels border on the limits of detectability. Collectively these parameters could account for the balance of unrecovered activity in the rat studies and a major portion of that in dogs. Even in a worst-case situation where dermal penetration data is corrected for incomplete urinary recovery based on comparable intravenous kinetics,[8] skin absorption of EDDN would still be considered minimal, i.e., 0.7 percent in rat and 2.5 percent in dogs.

12. CONCLUSIONS. On the basis of the data reported here, no recommendations regarding the hazard of human EDDN exposure can be made until corroborating systemic toxicity data in animals becomes available. Despite this limitation, some conclusions can be made. The skin absorption (bioavailability) of EDDN in man would be expected to be less than that observed in animals, probably less than 2 percent of a topical dose. Most absorption would occur within 48 hours. The primary elimination pathway of systemic EDDN is via urinary excretion; additional amounts may be eliminated in expired air. No marked potential for bodily accumulation of EDDN moieties has been observed in animals following a dermal application at 400 $\mu g/cm^2$. Some retention of the chemical may however, be expected in the body if rapid access to the systemic system is achieved.

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APPENDIX A

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APPENDIX B

ANALYTICAL QUALITY ASSURANCE

The Analytical Quality Assurance Office certifies the following:

a. These studies were conducted in accordance with:

(1) Standing Operating Procedures developed by the Toxicology Division, USAEHA.

(2) Title 21, Code of Federal Regulations (CFR), 1983 rev, Part 58, Good Laboratory Practice for Nonclinical Laboratory Studies.

(3) Final Rule, Pesticide Programs; Good Laboratory Practice Standards; 48 Federal Register (FR) 53946-53969, 29 November 1983.

(4) Final Rule, Toxic Substances Control; Good Laboratory Practice Standards; 48 Federal Register (FR) 53922-53944, 29 November 1983.

b. Facilities and testing procedures were inspected during its operational phase to ensure compliance with paragraph a above on 12, 19 and 19 April, and 9, 14, and 17 May 1984.

c. The information presented in this report accurately reflects the raw data generated during the course of conducting these studies.

Paul V. Sneeringer

PAUL V. SNEERINGER, Ph.D.
Chief, Analytical Quality
Assurance Office

APPENDIX C

TABLE C-1. EXCRETION OF RADIOACTIVITY FOLLOWING A SINGLE INTRAVENOUS INJECTION OF ^{14}C-LABELED EDDN IN RATS

PERCENT OF DOSE

Day	Urine	Feces
1	55.60 ± 6.51	1.44 ± 0.42
2	1.27 ± 0.16	0.37 ± 0.17
3	0.37 ± 0.05	0.10 ± 0.01
4	0.22 ± 0.02	0.02 ± 0.01
5	0.14 ± 0.02	0.01 ± 0.01
6	0.11 ± 0.01	< LLD
7	0.09 ± 0.01	< LLD
Total	57.80 ± 6.39	1.91 ± 0.56

LLD - Lower Limit of Detectability

RECOVERY OF RADIOACTIVITY 7-DAYS AFTER AN INTRAVENOUS INJECTION OF ^{14}C-LABELED EDDN IN RATS

SPECIMEN	PERCENT OF DOSE
Urine	57.80 ± 6.39
Feces	1.91 ± 0.56
Major Organs	1.19 ± 0.16
Carcass	11.28 ± 3.67
Total	72.18 ± 6.24

TABLE C-2. TISSUE DISTRIBUTION OF RADIOACTIVITY IN ANIMALS 7 DAYS AFTER A SINGLE INTRAVENOUS (I.V.) OR TOPICAL (P.C.) DOSE OF ^{14}C-EDDN

	Nanogram EDDN equiv./g tissue			
Tissue	Rat, i.v.	Rat, p.c.	Dog, i.v.	Dog, p.c.
Adrenal Gland	127.0 ± 45.1	<LLD	17.0 ± 2.3	0.3 ± 0.4
Bone	85.6 ±	<LLD	2.2 ± 2.0	<LLD
Bone Marrow	58.1 ± 14.1	11.4 ± 0.4	11.6 ± 6.2	<LLD
Brain	37.4 ± 3.5	2.3 ± 2.3	6.1 ± 4.2	<LLD
Fat	42.2 ± 5.9	<LLD	2.1 ± 0.8	<LLD
Heart	116.2 ± 17.1	28.9 ± 3.2	7.3 ± 3.6	0.2 ± 0.3
Kidney	143.4 ± 11.4	1.5 ± 0.3	45.5 ± 2.5	1.0 ± 0.7
Liver	242.7 ± 58.5	5.4 ± 2.9	35.1 ± 13.3	<LLD
Lung	105.2 ± 12.1	4.3 ± 4.3	7.7 ±5.1	<LLD
Muscle	89.9 ± 9.1	0.8 ± 0.8	13.5 ± 9.3	0.4 ± 0.6
Skin	141.3 ± 37.6	3.0 ± 0.7	8.6 ± 1.1	0.2 ± 0.2
Spleen	108.5 ± 7.0	0.7 ± 0.7	21.0 ± 14.8	0.8 ± 0.7
Testes	60.7 ± 16.2	<LLD	1.9 ± 2.7	<LLD
Thyroid Gland	---	---	18.9 ± 0.5	0.4 ± 0.6
Urinary Bladder	136.7 ± 11.6	1.4 ± 1.4	2.7 ± 1.5	<LLD
Terminal Blood	45.0 ± 4.7	1.1 ± 0.4	8.5 ± 0.8	0.4 ± 0.6
Bile	---	---	3.7 ± 1.1	0.2 ± 0.3

LLD. Lower Limit of Detectability

TABLE C-3. EXCRETION OF RADIOACTIVITY FOLLOWING A SINGLE INTRAVENOUS INJECTION OF ^{14}C-LABELED EDDN IN DOGS

PERCENT OF DOSE

Day	Urine	Feces
1	17.08 ± 4.86	0.32 ± 0.07
2	11.06 ± 4.53	0.34 ± 0.11
3	1.53 ± 0.73	0.21 ± 0.03
4	0.77 ± 0.36	0.09 ± 0.05
5	0.45 ± 0.07	0.05 ± 0.04
6	0.23 ± 0.06	0.03 ± 0.01
7	0.30 ± 0.24	0.02 ± 0.01
Total	31.42 ± 3.27	1.06 ± 0.09

RECOVERY OF RADIOACTIVITY 7-DAYS AFTER AN INTRAVENOUS INJECTION OF ^{14}C-LABELED EDDN IN DOGS

SPECIMEN	PERCENT OF DOSE
Urine	31.42 ± 3.27
Feces	1.06 ± 0.09
Major Organs	2.48 ± 1.04
Total	34.96 ± 4.88

TABLE C-4. URINARY EXCRETION OF RADIOACTIVITY FOLLOWING TOPICAL APPLICATION OF ^{14}C-LABELED EDDN IN DOGS AND RATS

PERCENT OF DOSE

Day	Dog, n = 3	Rat, n = 6
1	0.41 ± 0.33	0.24 ± 0.13
2	0.07 ± 0.05	0.05 ± 0.03
3	0.08 ± 0.07	0.03 ± 0.02
4	0.09 ± 0.02	0.01 ± 0.01
5	0.07 ± 0.02	0.02 ± 0.01
6	0.03 ± 0.03	0.01 ± 0.01
7	0.02 ± 0.02	0.02 ± 0.03
Total	0.77 ± 0.02	0.38 ± 0.16

TABLE C-5. FATE OF ^{14}C-LABELED EDDN 7-DAYS AFTER A SINGLE TOPICAL APPLICATION IN DOGS AND RATS

PERCENT OF DOSE

	Dog, n = 3	Rat, n = 6
Urine	0.77 ± 0.20	0.38 ± 0.16
Feces	< LLD	< LLD
Major Organs	0.04 ± 0.04	0.12 ± 0.04
Carcass	---	1.62 ± 0.74
Total Absorbed	0.81 + 0.32	2.12 + 0.76
24-Hour Patch	12.96 ± 11.06	21.64 ± 9.37
6-Day Patch	4.48 ± 2.46	12.84 ± 3.60
Skin - Appl Site	4.05 ± 3.03	15.58 ± 8.01
Recovered Unabsorbed	21.49 + 10.41	50.06 + 8.43